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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,101	GERRITSEN ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *15 -21, 32-35 and 46-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,22-31 and 36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group II, claims 1-14 and 22-27 in Paper No. 8 is acknowledged. Applicant traverse the Restriction Requirement on the grounds that: (i) the search of Groups I-XIII together would not constitute a serious search burden on the examiner and (ii) claims derected to antibody or immunoadhesin would be more properly addressed through an election of species.

This is not found persuasive because: (i) the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups. (ii) As was stated in the previous Office Action, methods comprising administrating immunoaghesin and antibody are distinct with respect to method steps and ingredients, therefore, each method is patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration, Claims of Group II (1-14 and 22-27) and IV (28-31 and 36-45) were rejoined and the prior art search has been extended to include claims 28-31 and 36-45.

Claims 15-21, 32-35 and 46-84 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-14 ,22-27, 28-31 and 36-45, as they read on the methods for controlling excessive proliferation of smooth muscle an method for treating stenosis comprising administering an effective amount of an antagonist of a native ErbB4 receptor, wherein antagonist is an antibody are under consideration in the instant application.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

4. The use of the trademark HERCEPTIN, page 4 line 18 and ENBREL, page 15, line 13 have been noted in this application. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.
Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1-14 , 22-27, 28-31 and 36-45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1 and 28 are indefinite and ambiguous in the recitation of "ErbB4 receptor" in the third line.
The use of " ErbB4 receptor " as the sole means of identifying the claimed receptor, without providing SEQ ID NO for the receptor protein renders the claim indefinite because " ErbB4" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely different receptor.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-14 , 22-27, 28-31 and 36-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of partially inhibiting proliferation or migration of smooth muscle cells in cell culture, comprising administering an effective amount of antibody to native ErbB4 receptor does not reasonably provide enablement for a method of a complete inhibiting proliferation or migration of smooth muscle cells *in vivo*, comprising administering an effective amount of antibody to native Erbb4 receptor and a method for treating or prevention stenosis in a mammalian patient comprising administering an effective amount of antibody to native ErbB4 receptor . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention

The specification only discloses that culturing human aortic smooth muscle cells in the presence of effective amount of antibody to native ErbB4 receptor reduces cell proliferation as was monitor by decreasing in the uptake of BrdU into said cell (Example 2) and reduces migration of said cells (Example 3). Based on the data shown in Fig. 5, that BrdU uptake was reduced about 20-30% after human aortic smooth muscle were incubated in the presence of antibody to native ErbB4 receptor , one skilled in the art at the time the invention was made would interpreted this results as partial but not total inhibition of proliferation. Applicant himself acknowledges that these examples only shown that only part of the mitotic and migration responses of said cell are mediated by the activation of the Erb4 receptor (page 68, lines 3-10 and 25-30 of the specification as filed). In other words, prevention of excessive proliferation and migration of smooth muscle cells even in cell culture was not be achieved by administration of antibody to native ErbB4 receptor. Moreover, since no animals were used as model system to treat stenosis it is not clear that reliance on the *in vitro* data that culturing human aortic smooth muscle cells in the presence of effective amount of antibody to native Erbb4 receptor will reduce cell proliferation as was monitor by decreasing in the uptake of BrdU into said cell (Example 2) and reduce migration of said cells (Example 3) accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively control excessive proliferation or migration *in vivo* or treat stenosis, or reach any therapeutic endpoint in mammals by administrating effective amount of antibody to native ErbB4 receptor. The specification does not teach how to extrapolate data obtained from an in vitro assay studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic package exemplified in the specification. In addition, Topol et al. (JAMA 278: 479-484, 1997) states that a large number of pharmacological agents have failed to reduce stenosis or restenosis or improve long-term clinical outcomes and that only the large-scale trial that reported an effect was using abciximab (see page 479, right hand column).

An effective protocol for controlling excessive proliferation or migration of smooth muscle cells *in vivo* or for treating stenosis comprising administering an effective amount of antibody to native ErbB4 receptor in the absence of *in vivo* clinical data are unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the antibody may not reach the target area because, i.e. the antibody may not be able to cross the mucosa or the antibody may be adsorbed by fluids, cells and tissues where the antibody has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Also, at issue is whether or not the claimed method would function to prevent of excessive proliferation(claimed in claim 2) or prevent stenosis (claimed in claim 42). The burden of

enabling the prevention of a disease (ie. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to stenosis within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Additionally, the specification fails to enable "treatment" to the extent such treatment includes the prevention of a disease state (e.g. see specification definition on page 13). Moreover, Menges et al. ,(Digestion, 2002, 65(3) p.184-189) teach that benefit of immunosuppressive therapy in the prevention of recurrent stenosis is not established. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

The specification does not provide sufficient teaching as to how it can be assessed that prevention of excessive proliferation in vivo and treating or prevention of stenosis was achieved after the administration of an effective amount of antibody to native ErbB4 receptor.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of a complete inhibiting proliferation or migration of smooth muscle cells *in vivo*, comprising administering an effective amount of antibody to native Erbb4 receptor and a method for treating or prevention stenosis in a mammalian patient comprising administering an effective amount of antibody to native ErbB4 receptor in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-3, 5-14 ,22-27, 28-31 and 36-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plowman et al. (US Paten 5,811,098) in view of Krymskaya et al (Am. J. Physiol.1999, 276, pages L246-L255) or Godowski et at .(WO 99/02681) and further in view of the known fact disclosed in specification of page 5, lines 7-25.

For examination purpose it is noted that , as pointed by Applicant, the term "ErbB4 receptor" is the same as the term "HER4 receptor" (page11, line 4 of the specification as filed).

US Patent '098 teaches a method of controlling excessive proliferation of cancer cells by administering an antibodies to native HER4 receptor (see entire document, Abstract in particular). US Patent '098 further teach that antibodies is a neutralizing antibody, chimeric, humanized or human antibody or glycosylated antibody (see columns 18-19 in particular). US Patent '098 also teach that said antibodies can be used to block signal transduction mediated through HER4 receptor, thereby inhibiting undesirable cell function and behaviors, including proliferation and migration (see column 22, lines 44-66 in particular). US Patent '098 teaches an amino-acid sequence of HER4 receptor (SEQ ID NO: 2) that is 100% identical to SEQ ID NO:2 of ErbB4 receptor of the current application (see attached sequence alignment).

US Patent '098 does not teaches a method of controlling excessive proliferation or migration of smooth muscle cells.

Krymskaya et al. teach the presence of ErbB4 receptor on the human airway smooth muscle cells (see entire document, abstract in particular). Krymskaya et al. teach that this receptor play a pivotal role in regulation of proliferation of smooth muscle cells and that uncontrolled proliferation of smooth muscle cells results in various pathologies and that regulation of proliferation of said cells has potential significance in treating said pathologies (see abstract and page L254 in particular).

Similarly , WO 99/02681 teaches the presence of ErbB4 receptor on smooth muscle cells and that blocking signal transduction pathway mediated through this receptor can effect mitotic activity of cells expressing said receptors (see entire document, page 8, lines 35 – 40 and page 17, lines 27-35 in particular).

The known fact disclosed in specification on page 5, lines 7-25 disclosed that excessive prolifetation of smooth muscle cells is involed in pathology of vascular stenosis, restenosis and hypertension and regulation of proliferation of said cells has potential significance in treating said pathologies.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Krymskaya et al ., or WO 99/02681 and known fact disclosed in specification on page 5, lines 7-25 to those of US Patent '098 to obtain a claimed method for controlling excessive proliferation or migration of smooth muscle cells and method for treating stenosis, comprising treating said cells with antibody to ErbB4 receptor.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because signal transduction mediated through ErbB4 receptor plays a pivotal role in regulation of proliferation of smooth muscle cells and uncontrolled proliferation of smooth muscle cells results in various pathologies and regulation of proliferation of said cells has potential significance in treating said pathologies as taught by combined teaching of Krymskaya et al. or WO 99/02681 and known fact disclosed in specification on page5, lines 7-25 . This uncontrolled proliferation can be blocked by a method taught by US Patent '098 using antibodies to ErbB4 receptor, that will block signal transduction mediated through ErbB4 receptor .

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 28-31 and 36-37 and 40-45 are included because it would have been obvious to a person of ordinary skill in the art at the time the invention was made that the same method that will control excessive proliferation or migration of smooth muscle cells can be also used for treating stenosis and additionally reduces hetertension associated with stenosis, caused by excessive proliferation or migration of smooth muscle cells.

Claims 26 -27 and 38-39 are included because total amino-acid sequence of ErbB4 receptor was known and it would have been obvious, conventional and within the skill of the art to make an antibody that will binds essentially the same epitope as an antibody recited in said claims.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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February 24, 2003

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